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EXAMINER	
PATEL, SUDHAKER B	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 05/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,238	RUMINISKI ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 related to compounds, composition and method of treatment are pending in this application.

First action on merits follows.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

The Office record shows that there is a PCT/USO1/30194 application, which also claims priority to U.S.Provisional Application Sr. No. 60235617 filed 9/27/2000 as claimed herein. See rejections bellow.

It is suggested that applicants update the record(s) for the instant application.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6720327. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant compounds of claims 1-4, compositions of claim 5, and method of use claim 6-7 overlap with the ref.'327 compounds claims 1-2, composition claim 3, method of use claims 4-5 respectively. See ref. Columns 50-54.

3. The ref.'327 differs from the instant claims by limiting the compounds to variable A = C. However, instant claims do not exclude the compounds, composition, and

method of use already patented. Therefore, if instant case is allowed, it will extend the monopoly of the patents already granted.

3A. Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10381834, filed 8/23/03. Although the conflicting claims are not identical, they are not patentably distinct from each other because ref.'834 claim 1 includes compounds, and all isomers, enasntiomers, automats, racemates and polymorphs thereof. Also, the ref.'834 claim 5 does not include a pharmaceutically acceptable carrier in the composition. Therefore, if the ref.'834 were granted patents rights, it would extend the monopoly of the instantly claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4.1. Claims 1,3-7 are rejected under 35 U.S.C. 102(e) as being anticipated by reference Ruminski et al (U.S.P. 6028223 filed as U.S. Application Sr. No. 08713555 on 8/27/1996 and it is claiming priority to U.S. Provisional Application Sr. No. 60003277 filed 8/30/1995.Note reference WO 9708145 also claims priority to Provisional U.S. Application Sr. No. 60003277 filed 8/30/1995.

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The instant application is related to various derivatives of 5-MEMBERED LACTONE (S) AND THEIR USE AS INTEGRIN ANTAGONISTS.

Reference '223 discloses making of many derivatives of lactones and use as alpha beta antagonists as claimed herein in the following manner:

-Examples in column 68 lines 15-30 describe the preparation of a precursor.

-Examples 188-191 in columns 173-174 describe the compounds with end hetero-ring having 1 or 2 N atoms as claimed herein.

-Example 226 in column 193 lines 45-68 recite the preparation of a lactones (= coumarone) and its hydrolysis to phenol propionic acid.

--Example 362 column 299 lines 15-30 recite making of 3-(1,4,5,6-tetrahydro)-5,5-dimethylpyrimidine-2-yl amino derivatives from the respective lactones, which are claimed herein.

-Example 393 in column recites making of **a five membered lactone** with phenyl ring as a substituent as claimed herein, and its hydrolysis to get the phenyl hydroxyl - butyric acid derivative.

-Example 394 in column 394 recites the making of Para-F substituted phenyl hydroxyl butyric acid from the lactones (which is claimed herein) by hydrolysis of these lactones.

-Example 399 in column 320 lines 20-43 recited making of propylene substituted 5-membered lactones and its hydrolysis to corresponding hydroxyl butyric acid.

-Examples 407-414 in columns 324-326 recite making of intermediates required for lactones.

-Examples 453-460 in columns 343-345 recite making of 5-membered lactones, which are claimed herein, and their hydrolysis to substituted hydroxyl- butyric acid.

Claim Rejections - 35 USC § 102

4.2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-7 are rejected under 35 U.S.C. 102(a) as being anticipate by Ruminski et al (WO 97 08145).

Reference'145 discloses making of many derivatives of lactones and use as alpha beta antagonists as claimed herein in the following manner:

-Example N on page 102 lines 1-19 describe the preparation of a precursor.

-Examples 188-191 on pages 331-334 describe the compounds with end heteroring having 1 or 2 N atoms as claimed herein.

-Example 226 on page 376 lines 1-26 recites the preparation of a lactone (= coumarone) and its hydrolysis to phenol propionic acid.

--Example 362 on page 588 lines 1-25 recite making of 3-(1,4,5,6-tetrahydro)-5,5-dimethylpyrimidine-2-yl amino derivative from the respective lactone.

-Example 393 on pages 624 627 recites making of **a five membered lactone** with phenyl ring as a substituent as claimed herein, and its hydrolysis to get the phenyl hydroxyl-butyric acid derivative.

-Example 394 on page 629 lines 1-15 recite the making of para-F substituted phenyl hydroxyl butyric acid from the lactone (which is claimed herein) by hydrolysis of this lactone.

-Examples 399 on page 631 lines 1-12 recite making of propylene substituted 5-membered lactone and its hydrolysis to corresponding hydroxyl butaric acid.

-Examples 407-414 on pages 639-641 recite making of intermediated required for lactones.

-Examples 453-460 on pages 658-660 recite making of 5-memberes for lactones and their hydrolysis to substituted hydroxyl butyric acid.

Preliminary examination also revealed that there are many applications claiming benefit to U.S. Provisional Application Sr. No. 60003277 filed 8/230/1995.

It will be necessary to review and examine these files during the prosecution of instant application. Applicants are also reminded of the fact that their disclosure of prior art(s) and their relevance to instant case is not complete.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply:

a). The amended claim 1 recites R1 as:" aryl". Specification on page 20 lines 22-25 defines aryl as phenyl and heterocycle(s) pyridine, thiophene, furan and the like. For this reason it is not very clear as to what applicants want to claim exactly and definitely. Correction is required. In re Sus et al., 135 USPQ 301 ; In re Lund et al.,153 USPQ 625.

b). The amended claim 1 recites "one or more substituents' for "alkyl optionally substituted", "aryl optionally substituted", "monocyclic heterocycles optionally substituted", "5-membered heteroaromatic ring optionally substituted"," 4-12 membered dinitrogen containing heterocycle optionally substituted". Therefore, it is not very clear as to what applicants want to present with "optionally substituted rings". Correction is required.

c). The amended claim 1 recites many duplication e.g. " aryl or aryl optionally substituted"," monocyclic heterocycles, and monocyclic heterocycles optionally substituted", "aryl, fused aryl, monocyclic heterocycles, or fused monocycles, aryl optionally substituted", "aryl, aralkyl, aryl optionally substituted". Correction is required for the reasons stated earlier in a)-b).

d). Amended Claim 1 recites variable Y' related to X, but Y' is not existing. Y1 is recited. Correction is required.

e) Amended claim 1 recites X as:" is a formula of paper (referred to earlier) wherein R1 and R8 taken together form 5-8 membered dinitrogen containing heterocycle optionally substituted with one or more substituent selected from the group consisting of "keto". It is not very clear as to what is to be substituted from the heteroicycle(s). It is not clear as to whether H of –CH, or Hydrogens of –CH2 or even a group –CH2- is to be substituted by a keto. Correction is required.

f). The last line(s) of amended claim 1 and independent claim 4 are recited as:" heterocycles; and all isomers, enantiomers, tautomers or polymorphs thereof". Correction(s) to:" heterocycles **or** isomers **or** enantiomers **or** tautomers **or** polymorphs thereof" are required.

g). Claim 4 is related to a compound selected from the group consisting of various molecules listed in the specification. The formulae listed in amendment pages 12-15

recite:"-CO-H-CH2-CO-NH- bridges(where applicable). Correction to proper chain(s) is required.

h). Claims 5 and 6 are related to a pharmaceutical composition and a method of use which are shown to be dependent on claims 1,2, 3 or 4, and claim 3 is also shown as dependent on claim 1. Claim 4 is recited as an independent claim. Therefore, it is not very clear as to what applicants want to claim exactly. Claim 1 can not support the structures of all the compounds as presented in independent claim 4. Correction is required.

i). Claim 5 is related to a pharmaceutical composition which does not recited its exact make up. Usually a pharmaceutically acceptable carrier is required. Correction is required.

j). Claim 6 recites the term:"a condition mediated". What is included by this term? Also, the claim does not recite the exact and definite step or process of administration.

k). Claims 2,3,7 are rejected because they are dependent on rejected claims.

Therefore, for the many reasons as stated earlier it would be difficult to practice the invention by one of ordinary skill.

Applicants are reminded that although the claims are interpreted in light of the specification, critical limitations from the specification cannot be read into the claims (see e.g. In re Van Guens, 988 F. 2d 1181, 26 PSPG 2d 1057 (Ded. Cir. 1991). Accordingly, without the recitation of all these critical limitations, the claims do not adequately define the instant invention.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for one single,definite and exact disease treatment, does not reasonably provide enablement for inhibiting a condition mediated by alphavbeta3 or alphavbeta5 integrin. The diseases include tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atheroscelosis, macular degeneration, retinopathy, arthritis and diseases yet to be discovered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

"Compound, all isomers, enantiomers, tautomers or polymorphs, and pharmaceutical composition(s) thereof as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carboxylic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1(or claims dependent on it) and/ or its pharmaceutical composition for treating a patient having diseases or conditions associated with tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atheroscelosis, macular degeneration, retinopathy, arthritis, and diseases yet to be discovered in general. Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their compositions as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art; ***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

1). The nature of the invention: The compounds and their method of use claim(s) are drawn in part to use them for treating a patient having diseases or conditions associated with tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atheroscelosis, macular degeneration, retinopathy, arthritis and diseases yet to be discovered.
2). The state of prior art: There are no known compounds of similar structure (i.e. compounds of invention that have been demonstrated for the treatment of infection or disease as recited here in a generic way.

3). The predictability or lack thereof in the art: It is presumed in the use for patient(s) who are humans or animals suffering from infection or disease related to activity of MMP inhibitors as claimed herein, there is a way of identifying those patient(s) who may develop any kind of physiological conditions including (but not limited to) a single disease. There is no evidence of record, which would enable the skilled artisan in the identification of the patient(s) who have the potential of becoming afflicted with the physiological conditions related to tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atheroscelosis, macular degeneration, retinopathy, arthritis and diseases yet to be discovered.

4). The amount of direction or guidance present and 5).: The presence or absence of working examples: There are no doses, and patient-dosage regime present to direct

one to treat a potential host from an infection or disease, and other multiples of physiologically related condition(s) of various types.

6). The breadth of the claims: The claims are drawn to physiological conditions (not limited to) for treatment of tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atheroscelosis, macular degeneration, retinopathy, arthritis and diseases yet to be discovered which are not related and whose treatment(s) is unknown by a compound of instant invention.

7). The quantity of experimentation need would be and undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

7. Discussion about Tumors/cancer(s);

For example, the claim sets forth not only for the treating tumor metastasis, but also for solid tumor growth and other diseases. However, there never has been a compound capable of treating various types of cancers. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancers and pain as recited earlier, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective anti-cancer agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologist today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. This is only for one of the many disorders as claimed herein.

Following references are quoted to show the state of art for Tumor/cancer:

- ***Cecil Textbook of Medicine*** states that: " each specific type of cancer has unique biological and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body.
  Also see In re Butting, 163, USPQ 689 (CCPA 1969), wherein "evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers".
- ***Structure-Based Design of Novel Anticancer Agent:***

Uckun et al(see Current Cancer Drug Targets, 1,59-71(2001) concludes in pages 66-67 that : " WHI-P131, which inhibits JAK3 but does not inhibit JAK1, JAK2, SYK,BTK,LYN or IRP even at concentrations as high as 350uM is undergoing further studies to evaluate its potential use as a new anti leukemic agent(in children). Agents that inhibit epidermal growth factor receptor(EGFR) may be useful for treatment of breast cancer. Tubulin modulating agents, which are of natural as well as synthetic origin, can be used as effective anticancer agents for treating breast cancer. COBRA compounds caused destruction of microtubule organization and apoptosis. Like other microtubule-interfering agents, COBRA compounds activated the proapoptotic c-Jun N-terminal kinase (JNK) signal transduction pathway, as evidenced by rapid induction of c-jun expression".

Following references are quoted to show the state of art for alpha/beta intewgrin subunits:

- ***The role of cytokines in osteoarthritis pathophysiology:***

Fernandes et al (PubMed Abstract12082286, also cited as Biorheology, 39/1-2, 237-46(2002) state that:"Several studies illustrate the potential importance of modulating IL-1 activity as a means to reduce the progression of the structural changes in OA.... Future directions in the research and treatment of OA will be based on the emerging picture of pathophysiological events that modulate the initiation and progression of osteoarthritis".

- **Distribution of alpha & beta inteigrin subunits in the adult rat:**

Faser et al(PubMed Abstract 12851778, also cited as Acta Neuropathol.(Berl).,106/4,319-22(2003)) state that:" Our result show that members of integrin family are differently distributed in cellular and subcellular compartments of the hippocampus and undergo specific patterns of regulation which may be important for lesion-induced reactive changes in the adult brain".

- ***Integrin structure: new twists and turns in dynamic cell adhesion:***

Arnaout MA.(PubMed Abstract 12234368, also cited as Immunol. Rev., 186,125-40(2002)) state that:" These structures also raise the tantalizing hypothesis that alphaA is regulated endogenousl integrin ligand, so that no special regulatory features are needed in this intergin. These findings provide the framework for new investigations of structure-activity relationships in integrins, with important implications for targeting these receptors therapeutically".

- ***Increased primary tumor growth in mice null for beta3- or beta3/beta5-integrins or selectins:***

Taverna et al(PunMed Abstract 1471870, also cited as Proc.Natl. Acad. Sci. USA 101/3,763-5(2004)) state that:" Tumor growth also was affected by bone marrow-derived cells in mice lacking any one or ...three selectins, implicating both leukocyte and endothelial selectind in tumor suppression".

- ***Effect/Use of existing drug(Dexamethasone) in normal human osteoblastic cells:***

Cheng et al(PubMed Abstract 10723092, also cited as Cell Biochem. 77/2,265-76(200)) state that:"Dex exhibited time-dependent regulation on the expression of alphabeta3 and alphabeta5 integrins in normal human osteoblastic cells. Short term exposure to Dex increased the levels of alphabets3 and alphabeta5 on surface and cell adhesion to osteopontin and vitronectin whereas long-term exposure to Dex decreased the expression of both integrins and inhibited the adhesion to matrix proteins".

- ***Alphabeta5 and retinopathy:***

Wilson et al(PubMed Abstract 12657612, also cited as Invest. Ophthalmol. Vis. Sci.,44/4,1704-15(2003)) state that:" Fn and its Fn-fs module HREC adhesion and proliferation through signal-transduction pathways involving coupling of the alpha5beta integrin through PI-3kinase. Mitogenic signals for endothelial cells from degraded extracellular matrix may contribute to the development of diabetic retinopathy".

8. Specification on pages 72-77 recites various test(s) and assay methods for binding activity of Vitronectin receptors. Results recited/summarized in lines 14-20 in page 77 state that:" The compounds evaluated were relatively ineffective at inhibition of alphavbeta6-mediated cell adhesion. The selective antagonism of the alphavbeta3 integrin is viewed as desirable in this class of compounds, as alphavbeta6 may also play a role in noprmal physiological processes of tissue repair and cellular turnover that routinely occur in the skin and pulmonary tissues".

These results will only serve for the preliminary screening of many compounds, and not for treating the diseases as claimed herein.

9. The facts as provided above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the method of treatment for various disorders/conditions related to inflammation, cancer, and other diseases.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of instant compounds to treat various disorders/diseases related to MMPs.

10. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is (571) 272-0671.

The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on (571) 272 0674 or Sr. Examiner Mr. Richard Raymond at (571) 272 0673 or Mr. James O. Wilson at (571) 272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sudhaker B. Patel, D.Sc. Tech.
May 7, 2004

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

MUKUND SHAH
SUPERVISORY PATENT EXAMINER
ART UNIT 1624/1623